REMARKS

Claims 1-6, 8-30, and 34-86 are pending in the present application. Claims 7, 9-12, 15-25, 31-49, and 53-86, have been canceled without prejudice or disclaimer. Claims 1-3, 8 and 50 have been amended. Claim 18 has been amended to make identify the specificity of the antibody termed "VD1." Support for the amendments is found throughout the specification. No new matter has been added by virtue of these amendments and their entry is respectfully requested.

Amendment and cancellation of the claims are not to be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or substantially similar claims, in this or one or more continuation patent applications.

Restriction Requirement

Page 2 of the Office Action indicates that claims 2-8, and 19-43 have been withdrawn as directed to non-elected subject matter. Applicants hereby reserve the right to pursue the subject matter of the cancelled claims in one or more divisional patent applications.

Claim Rejections Under 35 U.S.C. § 112.

Claim 18 is rejected under 35 U.S.C. § 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention..

Applicants respectfully traverse, however, in order to expedite prosecution the term "VD1" has been replaced by "anti-VEGF-D antibody." Support for the nomenclature, "VD1" is described, for example on page 27, lines 27-30: " VD1, a monoclonal antibody against the VHD of human VEGF-D, binds both unprocessed and fully processed VEGF-D and is able to block the interaction of VEGF-D with both VEGFR-2 and VEGFR-3" and on page 35 line 8: "detected in normal brain using an anti-VEGF-D antibody VD1."

Claim Rejections Under 35 U.S.C. § 103.

Claims 1, 9-11 and 13-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,235,713 B1 (filed Aug 1997; PTO 892) in view of U.S. Patent No. 5,874,290 (Feb 1999; PTO 892).

Applicants respectfully disagree and traverse the rejection.

Applicants invention is directed in part to the detection of cancer in a brain sample by detection of a VEGF-D marker. Applicant's teach the detection of VEGF-D is enhanced in malignant brain tissue and is aberrantly expressed in astrocytomas. Further, applicant's teach that VEGF-D is an X-linked factor and it would not be obvious that VEGF-D is expressed in brain tumors. (See for example, page 36 lines 15-33).

The Examiner acknowledges that the '713 patent differs from the instant invention in that the '713 patent does not teach or disclose that VEGF-D is detectable in brain tumors, nor does it suggest or disclose that VEGF-D is a potential tumor marker. The '713 patent provides no disclosure, teaching nor motivation to one of ordinary skill in the art, to examine brain tumors for the detection of the X-linked VEGF-D gene.

The Examiner alleges that "[t]he '713 patent teaches VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk." However, brain tumors, especially high grade gliomas are non-metastatic tumors, therefore detection of over-expressed VEGF-D in brain tissues is not an "indicator of future metastatic risk." Furthermore, the '713 patent in view of the '290 patent do not provide any teaching or motivation to one of ordinary skill in the art to combine the teachings of both patents and arrive at the instant invention.

The '290 patent does not teach or disclose that VEGF-D is over-expressed in tumors. VEGF was detected in some brain tumors but the '290 patent does not teach or disclose detection and over-expression of VEGF-D as a diagnostic marker of brain tumors. Further, the '290 patent

does not teach detection of over-expressed VEGF-D in brain tissue samples. The '290 patent utilized established cell lines for detection of the D2-2 gene. (See, for example, column 43, lines 49-62). Applicants submit that fetal brain tissue is not a tumor as suggested by the Examiner and consequently cannot be used as a tool to diagnose brain tumors. Considering the complexity of gene expression in cancer, especially genetic and epigenetic influences, the chromosomal localization of the genes and their promoter regions are important factors determining the levels of gene expression of various factors. In addition, the transcribed genes must be translated into proteins and this also occurs in a complex hard to predict manner in cancer cells. Considering that VEGFs have different chromosomal localizations, one of ordinary skill in the art would not expect that just because one type of VEGF is found in cancer, the detection of another factor is expected or obvious. See for example, the '713 patent column 2, lines 10-26. Therefore, the '713 patent in view of the '290 patent do not provide any suggestion, teaching or motivation to combine the teachings and arrive at the instant invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 12 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,235,713 B1 (filed Aug 1997; PTO 892) in view of U.S. Patent No. 5,874,290 (Feb 1999; PTO 892) as applied to claims 1, 9-11 and 17 and further in view of Stacker et al (J. Biol. Chem. 274(45):32127-32136; Nov 1999; PTO 1449) and Achen et al (Eur. J. Biochem. 267:2505-2515, May 2000; PTO 1449).

Applicants respectfully traverse.

As the Examiner has acknowledged on page 4, section 10 of the Office Action, claim 12 differs in that the proteolytic cleavage product comprises a VEGF-D homology domain and is detected in brain tissue samples using antibody, VD1.

Arguments regarding the combined teachings of '713 and '290 have been discussed *supra*, and for the sake of brevity will not be repeated here.

Neither Stacker et al, nor Achen et al, standing alone or in combination teach the detection of a VEGF-D homology domain in brain cancer. Since, a normal brain does not have a lymphatic system and GBM does not grow lymphatic vessel, applicants surprising discovery was the ubiquitous detection of the VEGF-D homology domain in the brain. None of the references teach the detection of VEGF-D in the brain nor, was the form of VEGF-D in the brain known prior to applicants invention. Use of the VD1 monoclonal antibody for "analyzing lymphangiogenesis" would not be applicable to a brain tumor for the reasons set forth above. The references of the '290 patent to "different types of brain tumors" has been discussed above, and the '713 patent regarding "future metastatic risk" is inapplicable for the reasons set forth above.

Accordingly, none of the combined teachings teach detection of the proteolytic cleavage product comprising a VEGF-D domain and detection thereof in brain tissue samples by VD1, due to a non-metastatic brain tumor. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-6, 8-30, and 34-86 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is accompanied by a petition for a one month retroactive extension of time and the required fee. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for a one month retroactive extension of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,

AKERMAN SENTERFITT

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